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(71) Applicant: **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, CH-4070 Basel (CH).

(72) Inventors: **FERTIG, Georg**; Wolfbauerweg 6, 82377 Penzberg (DE). **HERTING, Frank**; Frauenschuhstrasse 38, 82377 Penzberg (DE). **KUBBIES, Manfred**; Glaswandstrasse 7c, 82377 Penzberg (DE). **LIMBERG, Anja**; Würmseestrasse 58, 81476 München (DE). **REIFF, Ulrike**; Weidenweg 6, 82377 Penzberg (DE). **WEIDNER, Michael**; Ludwig-März-Strasse 39a, 82377 Penzberg (DE).

(74) Agent: **SCHREINER, Siegfried**; Roche Diagnostics GmbH, Patent Department (TR-E), Postfach 11 52, 82372 Penzberg (DE).

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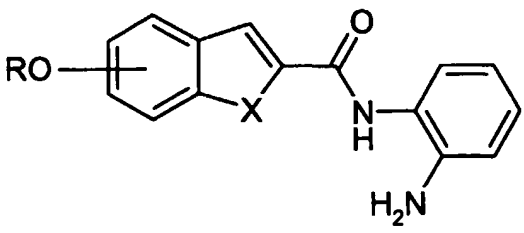
(54) Title: N-MONOACYLATED O-PHENYLENEDIAMINES AS ANTI -CANCER AGENTS



(I)

(57) Abstract: Objects of the present invention are new mono-acylated o-phenylendiamines derivatives of formula (I), wherein X represents N, S or O; R represents CH_3-(O-CH_2CH_2)n- or C_1-C_6-alkyl, which alkyl group is monosubstituted with -CO_2H, -OH, R^1R^2N-, pyridin-2-yl, pyrrolidin-1-yl, piperidino or morpholino; R^1, R^2 independently from each other denote C_1-C_6 alkyl; n is 1, 2, 3 or 4; and pharmaceutically acceptable salts thereof. The present invention also encompasses pharmaceutically acceptable salts or prodrugs of the compounds of formula I as well as the use of these compounds to produce medicaments.

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Novel N-Monoacylated o-phenylenediamines, their condensed heterocyclic derivatives and their use as pharmaceutical agents

The invention relates to novel antitumor agents and pharmaceutically acceptable acceptable salts thereof, processes for the manufacture of these novel compounds and medicaments, containing them. The compounds of the invention have antiproliferative and differentiation-inducing activity, which results in inhibition of tumor cell proliferation, induction of apoptosis and inhibition of invasion. The invention concerns thus also the use of such compounds for the treatment of diseases such as cancer and for the manufacture of corresponding medicaments.

Cancer is one of the major causes of death. Cancer exceeds heart and cerebrovascular diseases in causing death. Accordingly, many studies have been conducted with enormous expense and time to overcome cancer. However, despite a variety of therapies such as surgical operation, radiation therapy and chemotherapy, there is still a great need for improved anticancer therapeutics. Among these therapies, chemotherapy is one of the main areas for cancer treatment. Most drugs show their effect by inhibiting DNA from expressing their cytotoxicity and as a result, injuring tumor cells. However, chemotherapy lacks selectivity and consequently, does not sufficiently differentiate between tumor cells and normal cells, and therefore, adverse reactions expressed in normal cells have limited their use in therapy. Up to now, no satisfactory drugs are believed to have been discovered, and thus, an anticancer drug with reduced toxicity, better tolerability and a high therapeutic effect is very much desired.

The compounds according to this invention are inhibitors of histone deacetylase (HDAC) and therefore show antiproliferative and differentiation-inducing activity, which results in inhibition of tumor cell proliferation, induction of apoptosis and inhibition of invasion.

Transcriptional regulation is a major event in cell differentiation, proliferation, and apoptosis. Transcriptional activation of a set of genes determines cell destination and for this reason transcription is tightly regulated by a variety of factors. One of its regulatory mechanisms involved in the process is an alteration in the tertiary structure of DNA, which affects transcription by modulating the accessibility of transcription factors to their target DNA segments. Nucleosomal integrity is

regulated by the acetylation status of the core histones. In a hypoacetylated state, nucleosomes are tightly compacted and thus are nonpermissive for transcription. On the other hand, nucleosomes are relaxed by acetylation of the core histones, with the result being permissiveness to transcription. The acetylation status of the histones is governed by the balance of the activities of histone acetyl transferase (HAT) and histone deacetylase (HDAC). Recently, HDAC inhibitors have been found to arrest growth and induce apoptosis in several types of cancer cells, including colon cancer cells, T-cell lymphoma cells, and erythroleukemic cells. Given that apoptosis is a crucial factor for cancer progression, HDAC inhibitors are promising reagents for cancer therapy as effective inducers of apoptosis (Koyama, Y., et al., Blood 96 (2000) 1490-1495).

The compounds of the present invention surprisingly show low toxicity, together with a potent anti-proliferative and cell differentiation activity characterized by enhanced acetylation due to inhibition of HDAC.

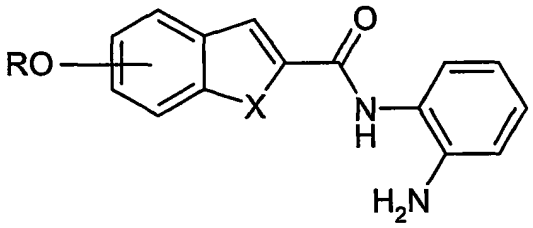
EP-A 0 847 992 describes monoacylated o-phenylendiamine derivatives as cell differentiation inducers. The same type of compounds is also the subject of EP-A 0 242 851. The compounds described in these applications are almost exclusively o-phenylene derivatives monoacylated with derivatives of benzoic acid. However, there is still a need to provide compounds with improved properties such as increased tolerability, less toxicity and less side effects.

Monoacylated o-phenylendiamines are known in the art as precursors for the preparation of the corresponding benzimidazoles, such preparation methods are e.g. described in DE-A 2 062 265; FR 2 167 954; Rastogi, R., and Sharma, S., Indian J. Chem., Sect. B, 21B (5) (1982) 485-487; Moll, R., et al., Z. Chem. 17 (1977) 133-134; and Hassan, H., et al., Indian J. Chem. 39B (2000) 764-768.

It has been found that the compounds of the present invention are HDAC inhibitors which have anti-proliferative and differentiation-inducing activity, which results in inhibition of tumor cell proliferation, induction of apoptosis and inhibition of invasion. These compounds are therefore useful for the treatment of diseases such as cancer in humans or animals. Examples of tumors which may be treated, but are not limited to, colon cancers, breast carcinoma (including advanced breast cancer), lung cancer (e.g. adenocarcinoma and including non-small cell lung cancer), prostate cancer including advanced disease, pancreatic cancers,

hematopoetic tumors of lymphoid lineage (e.g. acute lymphotic leukemia, B-cell lymphoma, Burkitt's lymphoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MSD), tumors of mesenchymal origin, melanomas, teratocarcinomas, neuroblastomas, gliomas, benign tumors of the skin (e.g. keratoacanthomas), kidney carcinoma, ovary carcinoma, bladder carcinoma and epidermal carcinoma.

In particular, the present invention concerns compounds of the general formula I



(formula I),

wherein

X represents N, S or O;

R represents CH_3-(O-CH_2CH_2)n- or C_1-C_6-alkyl, which alkyl group is monosubstituted with
-CO_2H, -OH, R^1R^2N-, pyridin-2-yl, pyrrolidin-1-yl, piperidino or morpholino;

R^1, R^2 independently from each other denote C_1-C_6 alkyl;

n is 1, 2, 3 or 4;

and pharmaceutically acceptable salts thereof.

The present invention also encompasses pharmaceutically acceptable salts or prodrugs of the compounds of formula I as well as the use of these compounds to produce medicaments.

The term "C_1-C_6-alkyl" as used herein denotes a saturated, linear- or branched chain alkyl group containing 1 to 6 carbon-atoms, for example methyl, ethyl, propyl, isopropyl, 1-butyl, 2-butyl, tert-butyl and the like. Preferred "C_1-C_6-alkyl" groups have 1, 2 or 3 carbon-atoms.

Compounds of the general formula I can contain one or several chiral centers and can then be present in a racemic or in an optically active form. The racemates can

be separated according to known methods into the enantiomers. Preferably, diastereomeric salts which can be separated by crystallization are formed from the racemic mixtures by reaction with an optically active acid such as e.g. D- or L-tartaric acid, mandelic acid, malic acid, lactic acid or camphorsulfonic acid.

The compounds according to the present invention may exist in the form of their pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of formula I and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Acid-addition salts include for example those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as p-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethylammonium hydroxide. The chemical modification of a pharmaceutical compound into a salt is a technique well known to pharmaceutical chemists in order to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. It is for example described in Ansel, H., et. al., In: Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th ed. (1995), pp. 196 and 1456-1457.

A preferred embodiment of the invention are compounds of formula I, wherein

X represents N, S or O;

R represents R^1R^2N-(C_1-C_6)-alkyl; and

R^1, R^2 are independently a C_1-C_6-alkyl group such as for example

5-(2-Dimethylamino-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide,

5-(3-Dimethylamino-propoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide,

7-(3-Dimethylamino-propoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide,

5-(3-Dimethylamino-propoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide,

7-(2-Dimethylamino-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide,
7-(2-Diisopropylamino-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide, or
5-(2-Diisopropylamino-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide.

A further preferred embodiment of the invention are compounds of formula I, wherein

X represents N, S or O;
R represents a group alkyl-$(O\text{-}CH_2CH_2)_n$-;
n is 1, 2, 3 or 4; such as for example
5-(2-Methoxy-ethoxy)-1H-indole-2-carboxylic acid (2-amino-phenyl)-amide,
5-(2-Methoxy-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
7-(2-Methoxy-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide,
7-[2-(2-Methoxy-ethoxy)-ethoxy]-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide,
5-[2-(2-Methoxy-ethoxy)-ethoxy]-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide.

A further preferred embodiment of the invention are compounds of formula I, wherein

X represents N, S or O;
R represents C_1-C_6-alkyl, monosubstituted with
pyridin-2-yl, pyrrolidin-1-yl, piperidino, morpholino; such as for example
7-(Pyridin-2-ylmethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide,
5-(Pyridin-2-ylmethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
7-(2-Pyrrolidin-1-yl-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide,

7-(2-Piperidin-1-yl-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide,
5-(2-Morpholin-4-yl-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide.

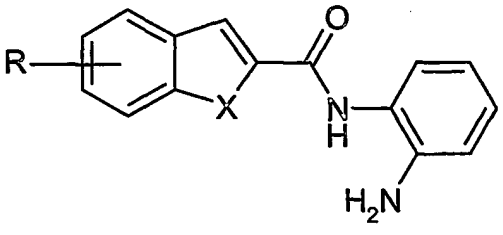
A further preferred embodiment of the invention are compounds of formula I, wherein

X represents N, S or O;
R represents C_1-C_6-alkyl, monosubstituted with -CO_2H; such as for example
2-(2-Amino-phenylcarbamoyl)-benzofuran-7-yloxy]-acetic acid,
2-(2-Amino-phenylcarbamoyl)-benzo[b]thiophene-5-yloxy]-acetic acid,
2-(2-Amino-phenylcarbamoyl)-1H-indole-5-yloxy]-acetic acid.

A further preferred embodiment of the invention are compounds of formula I, wherein

X represents N, S or O;
R represents C_1-C_6-alkyl, monosubstituted with OH; such as for example
5-(2-Hydroxy-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-(2-Hydroxy-ethoxy)-1H-indole-2-carboxylic acid (2-amino-phenyl)-amide
or
7-(2-Hydroxy-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide.

Another embodiment of this invention are compounds of the formula I-A



(formula I-A),

wherein

X and R have the significance given herein before;

and pharmaceutically acceptable salts thereof.

A preferred embodiment of this invention are compounds of formula I-A, wherein

X represents O;

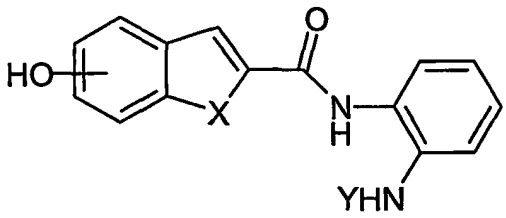
R is C_1-C_6-alkyl, which alkyl group is monosubstituted with –OH.

Such a compound is, for example,

5-(2-Hydroxy-ethyl)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide.

A further embodiment of this invention is a process for the manufacture of the o-phenylenediamine derivatives of the general formula I, comprising

a) reacting a compound of formula II



(formula II),

in which

X is as defined above; and
Y represents hydrogen or a suitable amino protecting group

with a compound of formula III

R-LG

(formula III),

in which

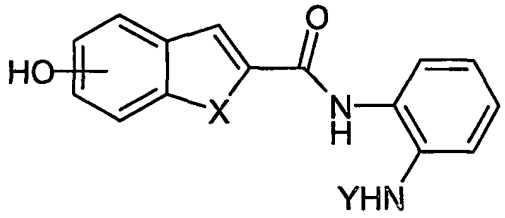
R has the meaning described above; and
reactive substituents, if present in R, are suitably protected;
LG is a suitable leaving group; and

b) subsequently if Y respesents a protected amino group, deprotection of this group as well as cleavage of protecting groups, if present, in R to give a compound of formula I; and

c) conversion, if desired, into its pharmaceutically acceptable salt.

An o-phenylene diamine derivative of the formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare an o-phenylene diamine derivative of the formula I, or a pharmaceutically-acceptable salt thereof, are provided as a further feature of the invention and are illustrated by the following representative examples in which, unless otherwise stated, X, R, R^1 and R^2 , n have the meanings defined above. Starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described within the accompanying examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

(a) Compounds of formula I are prepared from compounds of the formula II



(formula II)

wherein X is as defined above and wherein Y represents hydrogen or a suitable amino protecting group. Protection groups for the amino group are known from peptide chemistry, such protecting groups are for example, benzyloxycarbonyl (cleavage by hydrogenation or hydrobromic acid in acetic acid), t-butoxycarbonyl (cleavage by strong acids, such as, trifluoroacetic acid neat or in dichloromethane, or HCL in dioxane), 9-fluorenmethoxycarbonyl (cleavage by secondary amines, such as, piperidine).

The alcohol of formula II can be converted into an OR-group for example by a substitution reaction with a compound of the general formula III

R-LG (formula III)

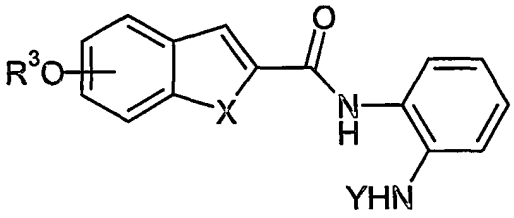
Wherein LG is a suitable leaving group for this substitution; examples for LG are Br, Cl, I, tosylate, mesylate.

Wherein R is as defined above and reactive substituents, if present, are suitably protected e.g. a carboxylate substituent is protected for example as the corresponding methyl-, ethyl-, t-butyl-, benzyl or p-methoxybenzyl-ester. A hydroxy substituent is protected for example as the corresponding methyl-, benzyl, tetrahydropyranyl- ethoxyethyl- or silylether.

The reaction is carried out in an inert solvent, for example in methanol, ethanol, acetonitrile, ethyl acetate, dimethylsulfoxide (DMSO), dimethylformamide (DMF) and preferably in the presence of a base, e.g. potassium carbonate (K_2CO_3), sodium hydroxide (NaOH), triethylamine, sodium hydride (NaH). If necessary the reaction mixture is heated.

After the alkylation reaction Y and other protecting groups finally have to be cleaved (methods see above) to yield compound I.

The compounds of the formula II can be obtained be cleavage of the R^3 group of compounds of the formula IV

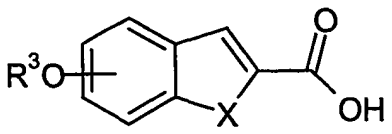


(formula IV)

wherein R^3 is an alkyl, alkenyl, silyl, optionally substituted benzyl or acyl group. The cleavage of an allyl group can be accomplished for example by a palladium

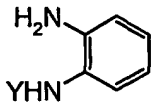
catalyzed reaction in methanol/water in the presence of catalytic amount of p-toluenesulfonic acid. The cleavage of an benzoyl group can be accomplished by sodium methoxide in methanol .

A preferred method for the preparation of compounds of the formula IV is the reaction of acids of the formula V



(formula V)

with a compound of the formula VI



(formula VI)

wherein R^3, X and Y are as defined above.

This reaction typically involves a two-step one-pot procedure. In the first step, the carboxylate of the formula V is activated by reaction of the compound in an inert solvent or diluent, for example, in dichloromethane, dioxane, or tetrahydrofuran, in the presence of an activating agent.

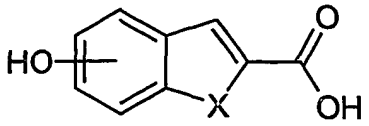
A suitable reactive derivative of an acid is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride or oxalic acid dichloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol; an active ester formed by the reaction of the acid and N-hydroxybenzotriazole; an acyl azide, for example an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the

reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide such as N-3-dimethylaminopropyl-N-ethylcarbodiimid or dicyclohexylcarbodiimide; or the product of the reaction of the acid with N,N'-carbonyldiimidazole; or the product of the reaction of the acid and uroniumsalts such as O-(1H-benzotriazol-1-yl)-N,N,N',N',-tetramethyluronium tetrafluoroborate; or the product of the reaction of the acid and phosphorus based reagents, e.g. bis-(2-oxo-3-oxazolidinyl)-phosphorylchloride. The reaction is carried out between -30°C and 60°C, conveniently at or below 0°C. In the second step, compound VI is added to the solution to yield compound IV.

These methods are well known to those skilled in the art. In principle, all methods for the synthesis of amides as used in peptide chemistry as described in e.g. Houben-Weyl, Methoden der organischen Chemie, Vols. XV/1 and XV/2 are also applicable. Monoacylation of unprotected phenylene diamine is described in EP 0 974 576.

There are quite a few compounds of formula V described in the literature. For example, the 5-Allyloxy-1H-indole-2-carboxylic acid is described in Moody, C.J., J. Chem. Soc. Perkin Trans. 1 (1984) 1333-1337; Julia, M., and Lallemand, J.-Y., Bull. Soc. Chim. Fr. (1973) 2046-2057.

In other cases compounds of formula V can be prepared by alkylation, silylation or acylation of compounds of formula VII



(formula VII)

E.g. a benzoylation can be accomplished for example with benzoyl chloride in dichloromethane in the presence of pyridine.

There are quite a few compounds of formula VII described in the literature. For example, 5-Hydroxy-benzo[b]thiophene-2-carboxylic acid is described in Misra, T., et al., Spectrochim. Acta Part A 57 (2001) 2795-2808; 7-Hydroxy-benzofuran-2-carboxylic acid is described in Reichenstein, Helv. Chim. Acta 18 (1935) 816, 826.

The compounds according to the general formula I-A can be synthesized as exemplified in detail for 5-(2-Hydroxy-ethyl)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (Example 24), and by using the respective starting materials. Therefore the manufacture of the compounds according to the general formula I-A as well as the synthesis of the respective starting materials is within the ordinary skills of an organic chemist.

The compounds of formula I and I-A, as well as their pharmaceutically usable addition salts possess valuable pharmacological properties. It has been found that they possess antiproliferative and differentiation-inducing activity, which results in inhibition of tumor cell proliferation, induction of apoptosis and inhibition of invasion. Therefore these compounds are useful for the treatment of diseases such as cancer in humans or animals. Consequently a further embodiment of the present invention is the use of a compound of formula I or I-A for the treatment of cancer. Yet another embodiment is the use of a compound of formula I or I-A for the manufacture of corresponding medicaments for the inhibition of tumor growth.

The activity of the compounds according to this invention as HDAC inhibitors is demonstrated using a cellular acetylation assay. Therein acetylation of histones is monitored in PC3 cells. High acetylation correlates with inhibition of histone deacetylase by compounds. Cell viability is monitored in parallel to estimate the cytotoxicity of compounds.

PC3 cells, a human prostate carcinoma cell line, are seeded as 1800 cells per well of a 384-well microtiterplate in RPMI 1640 (including 5% FCS, 2mM glutamine and pen / strep).

After 48 h at 37 °C pre-diluted compounds are added to a final concentration of 1 uM. Compounds are pre-diluted in dimethyl sulfoxide (DMSO) resulting in a final concentration of DMSO of 0.5 % per well.

After 24 h incubation cell viability is determined by adding cell proliferation reagent WST-1 (Roche Molecular Biochemicals). Another 60 min later the optical density (OD) is measured (450 nm versus 690 nm).

After measurement the cell layer is prepared for the ELISA reaction. Medium is aspirated and cells are fixed in ethanol at –20 °C for 60 min. After washing with

PBS / Tween the blocking solution (PBS/ 5% FCS / Tween) is added and the cell layer is washed again. Antibodies against acetylated histone H3 or H4 (rabbit polyklonal IgG, Upstate Biotechnologie) are added at a dilution of 1:200 for 60 min at 37 °C. As a second antibody goat anti rabbit IgG (H+L) humanIgG adsorbed-HRP conjugate (Dako) is used (1:2000 diluted). Cells are washed 3 times and the peroxidase substrate ABTS is allowed to react for 30-60 min at 37 °C. The OD is measured at 405 nm.

The percentage of acetylation is calculated after substraction of blank O.D.s:

$$\frac{\dfrac{\text{mean O.D. acetylation}}{\text{mean O.D. DMSO control}}}{\dfrac{\text{mean O.D. WSTI}}{\text{mean O.D. DMSO control}}} \times 100\%$$

Ex.-No.	Compound Name	cell acetylation (PC3, 1 µM) [% of control]
	4-acetylamino-N-(2-amino-phenyl)-benzamide (Reference Compound from EP0242851, Example 1)	152
2	5-(3-Dimethylamino-propoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide	209
3	5-(2-Diisopropylamino-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide	172
16	5-(2-Hydroxy-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide	156
24	5-(2-Hydroxy-ethyl)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide	157

The effect of the compounds according to the present invention may further be assessed by the following test:

Male NMRI nu/nu-mice(n = 15 per group), aged 8-10 weeks, were subcutaneously injected with 5*106 PC-3 prostate carcinoma cells. On day 10, animals with tumor volumes of about 150 mm^3 were randomly assigned to treatment groups. The test compound was administered as a microsuspension in 7,5% gelatine - 0,22% NaCl-Suspension with an application volume of 10 ml/kg based on actual body weights.

Once daily oral treatment was performed from approximately day 10 to day 27 on a, 5-7 times per week treatment schedule.

The volume of the tumor is determined from the following equation:

Volume of a tumor = $1/2ab^2$, where "a" and "b" are the long and the short diameters of the tumor, respectively

Yet another embodiment of the invention is a medicament containing as an active ingredient a compound of formula I or I-A as described herein before, if desired together with pharmaceutically acceptable adjuvants. Said medicaments, e.g. in the form of pharmaceutical preparations, can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The above-mentioned pharmaceutical preparations can be obtained by processing the compounds according to this invention with pharmaceutically inert, inorganic or organic carriers. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparations can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

Preferred pharmaceutical preparations comprise the following:

a) Tablet Formulation (Wet Granulation):

Item	Ingredients	mg/tablet			
1.	Compound of formula I or I-A	5	25	100	500
2.	Lactose Anhydrous DTG	125	105	30	150
3.	Sta-Rx 1500	6	6	6	30
4.	Microcrystalline Cellulose	30	30	30	150
5.	Magnesium Stearate	1	1	1	1
	Total	167	167	167	831

Manufacturing Procedure:

1. Mix items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50°C.
3. Pass the granules through suitable milling equipment.
4. Add item 5 and mix for three minutes; compress on a suitable press.

b) Capsule Formulation:

Item	Ingredients	mg/capsule			
1.	Compound of formula I or I-A	5	25	100	500
2.	Hydrous Lactose	159	123	148	---
3.	Corn Starch	25	35	40	70
4.	Talc	10	15	10	25
5.	Magnesium Stearate	1	2	2	5
	Total	200	200	300	600

Manufacturing Procedure:

1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

c) Formulation as a Micro-Suspension:

Weigh 4.0 g glass beads in custom made tube GL 25, 4 cm (the beads fill half of the tube).
Add 50 mg compound of formula I or I-A, disperse with spatulum and vortex.
Add 2 ml gelatin solution (weight beads: gelatin solution = 2:1) and vortex.
Cap and wrap in aluminium foil for light protection.
Prepare a counter balance for the mill.
Mill for 4 hours, 20/s in a Retsch mill (for some substances up to 24 hours at 30/s).
Extract suspension from beads with two layers of filter (100 µm) on a filter holder, coupled to a recipient vial by centrifugation at 400 g for 2 min.
Move extract to measuring cylinder.
Repeat washing with small volumes(here 1 ml steps) until final volume is reached or extract is clear.
Fill up to final volume with gelatin and homogenise.

The dosage depends on various factors such as manner of administration, species, age and/or individual state of health. The doses to be administered daily are about 5-400 mg/kg, preferably about 10-100 mg/kg, and can be taken singly or distributed over several administrations.

The invention will now be illustrated in the following examples in which, unless otherwise stated:

i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;
(ii) operations were carried out at ambient temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;
(iii) column chromatography (by the flash procedure) and high pressure liquid chromatography (HPLC) were performed on Merck Kieselgel silica or Merck Lichroprep RP-18 reversed-phase silica obtained from E. Merck, Darmstadt, Germany;
(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) melting points were determined using a Mettler SP62 automatic melting point apparatus, an oil-bath apparatus or a Kofler hot plate apparatus;
(vi) the structures of the products of the formula I were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques (Micromass Platform II machine using APCI or Micromass Platform ZMD using electrospray);
(vii) intermediates were not generally fully characterized and purity was assessed by thin layer chromatography;

(viii) the following abbreviations have been used:

DMF	N,N-dimethylformamide;
DMSO	dimethylsulphoxide;
THF	tetrahydrofuran;
MeOH	methanol;
HCl	hydrochloric acid;
NaH	sodium hydride
CH_2Cl_2	dichloromethane;
H_2SO_4	sulphuric acid
sat.	saturated
sol.	solution
h	hour
d	days
rt	room temperature
eq	equivalent
mp	melting point [°C] .
MW calc'd	molecular weight, calculated [g/mol]
MW found	molecular weight, determined by mass spectrometry [g/mol]

Example 1

5-(2-Dimethylamino-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (1)

Step 1: *O*-Benzoyl-5-hydroxybenzothiophene-2- carboxylic acid (2)

To a suspension of 1168mg (6.01 mmol) 5-Hydroxy-benzo[*b*]thiophene-2-carboxylic acid (Misra, T., et al., Spectrochim. Acta Part A 57 (2001) 2795-2808) in 30ml dichloromethane were added 1186mg (15mmol) pyridine. The mixture was

cooled to 0°C and a solution of 1968mg (14mmol) benzoyl chloride in 15ml dichloromethane was added within 0.5h. The reaction mixture was warmed to room temperature and added to 5% aqueous citric acid. The aqueous phase was extracted twice with dichloromethane, the solvent of the organic phases was removed and the residue was chromatographed on silica gel (dichloromethane/methanol 19:1 and then dichloromethane/methanol 19:1 with 2% acetic acid) to yield 1180mg (3.96mmol) *O*-Benzoyl-5-hydroxybenzothiophene-2-carboxylic acid (2) as colorless crystals, mp.235-236°C.

Step 2: Benzoic acid 2-(2-*tert*-butoxycarbonylamino-phenylcarbamoyl)-benzo[*b*]thiophen-5-yl ester (3)

To a suspension of 598mg (2mmol) *O*-Benzoyl-5-hydroxybenzothiophene-2-carboxylic acid (2) in 25ml toluene at 80°C DMF was added dropwise until the mixture became clear. 420mg (3.5mmol) thionyl chloride were added. After 4h at this temperature the solvent of the reaction mixture was removed. The residue was dissolved in 20ml dichloromethane and 1.0ml pyridine and a solution of 396mg mono-boc-orthophenylenediamine in 10ml dichloromethane were added. After 12h the reaction solution was poured on 5% aqueous citric acid. Extraction with dichloromethane, washing of the organic phase with aqueous citric acid and brine. The organic phase was dried over sodium sulfate, the solvent was evaporated and the residue subjected to silica gel chromatography (petrolether/ethylacetate 3:1). Benzoic acid 2-(2-*tert*-butoxycarbonylamino-phenylcarbamoyl)-benzo[*b*]thiophen-5-yl ester (3) was recrystallized from ethyl acetate to yield 790mg (1.62mmol) as colorless crystals, mp.205-208°C (decomp.).

Step 3: {2-[(5-Hydroxy-benzo[*b*]thiophene-2-carbonyl)-amino]-phenyl}-carbamic acid *tert*-butyl ester (4)

To a suspension of 732mg (1.5mmol) benzoic acid 2-(2-*tert*-butoxycarbonylamino-phenylcarbamoyl)-benzo[*b*]thiophen-5-yl ester (3) in 30ml methanol was added 1.0ml of a 5.4M solution of NaOMe in methanol. After 3h at room temperature the reaction solution was poured on 5% aqueous citric acid. Extraction with ethyl acetate, washing of the organic phase with brine. The organic phase was dried over sodium sulfate, the solvent was evaporated and the residue subjected to silica gel chromatography (petrolether/ethyl acetate 3:1). {2-[(5-Hydroxy-benzo[*b*]thiophene-2-carbonyl)-amino]-phenyl}-carbamic acid *tert*-butyl ester (4)

was recrystallized from ethyl acetate/ diethyl ether to yield 546mg (1.42mmol) as colorless crystals, mp.185°C (decomp.).

Step 4: (2-{[5-(2-Dimethylamino-ethoxy)-benzo[b]thiophene-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (5)

To a solution of 77mg (0.20mmol) {2-[(5-Hydroxy-benzo[*b*]thiophene-2-carbonyl)-amino]-phenyl}-carbamic acid *tert*-butyl ester (4) in 3ml ethyl acetate was added 120 mg potassium carbonate and 36mg (0.25mmol) (2-chloro-ethyl)-dimethyl-amine hydrochloride. The reaction mixture was heated at reflux for 16h and poured into brine. The aqueous phase was extracted with ethyl acetate and the organic phase was dried over sodium sulfate, the solvent was evaporated and the residue subjected to silica gel chromatography (dichloromethane/methanol 19:1 and then 9:1). (2-{[5-(2-Dimethylamino-ethoxy)-benzo[b]thiophene-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (5) (72mg, 0.158mmol) was obtained as a colorless solid.

Step 5: 5-(2-Dimethylamino-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (1)

A solution of 72mg (0.158mmol) (2-{[5-(2-Dimethylamino-ethoxy)-benzo[b]thiophene-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (5) in 1.0ml trifluoroacetic acid was stirred for 60min at room temperature and then added to an aqueous solution of sodium bicarbonate. After extraction with ethyl acetate and removal of the solvent the residue was recrystallized from ethyl acetate/ diethyl ether to yield 35mg (0.10mmol) 5-(2-Dimethylamino-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (1) as a yellow solid, mp.191-193°C.

Example 2

5-(3-Dimethylamino-propoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (6)

Step 1: (2-{[5-(3-Dimethylamino-propoxy)-benzo[b]thiophene-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (7)

(7) is prepared from {2-[(5-Hydroxy-benzo[*b*]thiophene-2-carbonyl)-amino]-phenyl}-carbamic acid *tert*-butyl ester (4) in an analogous manner to that described for the preparation of (5) example 1, step 4.

Step 2: 5-(3-Dimethylamino-propoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (6)

(6) is prepared from (2-{[5-(3-Dimethylamino-propoxy)-benzo[b]thiophene-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (7) in an analogous manner to that described for the preparation of (1) example 1, step 5; white solid, mp. 164-167°C.

Example 3

5-(2-Diisopropylamino-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (8)

Step 1: (2-{[5-(2-Diisopropylamino-ethoxy)-benzo[b]thiophene-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (9)

(9) is prepared from {2-[(5-Hydroxy-benzo[*b*]thiophene-2-carbonyl)-amino]-phenyl}-carbamic acid *tert*-butyl ester (4) in an analogous manner to that described for the preparation of (5) example 1, step 4.

Step 2: 5-(2-Diisopropylamino-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (8)

(8) is prepared from (2-{[5-(2-Morpholin-4-yl-ethoxy)-benzo[b]thiophene-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (9) in an analogous manner to that described for the preparation of (1), example 1, step 5; yellow solid.

Example 4

5-(2-Morpholin-4-yl-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (10)

Step 1: (2-{[5-(2-Morpholin-4-yl-ethoxy)-benzo[b]thiophene-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (11)

(11) is prepared from {2-[(5-Hydroxy-benzo[*b*]thiophene-2-carbonyl)-amino]-phenyl}-carbamic acid *tert*-butyl ester (4) in an analogous manner to that described for the preparation of (5) example 1, step 4.

Step 2: 5-(2-Morpholin-4-yl-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (10)

(10) is prepared from (2-{[5-(2-Morpholin-4-yl-ethoxy)-benzo[b]thiophene-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (11) in an analogous manner to that described for the preparation of (1) example 1, step 5; white solid, mp. 166-169°C.

Example 5

7-(2-Dimethylamino-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (12)

Step 1: 7-Benzoyloxy-benzofuran-2-carboxylic acid (13)

(13) is prepared from 7-Hydroxy-benzofuran-2-carboxylic acid (Reichenstein, Helv.Chim.Acta, 1935, 18, 816, 826.) in an analogous manner to that described for the preparation of (2) example 1, step 1, mp. 251-253°C (subl.).

Step 2: Benzoic acid 2-(2-tert-butoxycarbonylamino-phenylcarbamoyl)-benzofuran-7-yl ester (14)

(14) is prepared from 7-Benzoyloxy-benzofuran-2-carboxylic acid (13) in an analogous manner to that described for the preparation of (3) example 1, step 2, mp. 206°C (subl.).

Step 3: {2-[(7-Hydroxy-benzofuran-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (15)

(15) is prepared from benzoic acid 2-(2-tert-butoxycarbonylamino-phenylcarbamoyl)-benzofuran-7-yl ester (14) in an analogous manner to that described for the preparation of (3) example 1, step 3, mp. 168°C (decomp.).

Step 4: (2-{[7-(2-Dimethylamino-ethoxy)-benzofuran-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (16) .

(16) is prepared from {2-[(7-Hydroxy-benzofuran-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (15) in an analogous manner to that described for the preparation of (5) example 1, step 4.

Step 5: 7-(2-Dimethylamino-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (12)

(12) is prepared from (2-{[7-(2-Dimethylamino-ethoxy)-benzofuran-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (16) in an analogous manner to that described for the preparation of (1) example 1, step 5; white solid, mp. 108-118°C.

Example 6

7-(3-Dimethylamino-propoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (17)

Step 1: (2-{[7-(3-Dimethylamino-propoxy)-benzofuran-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (18)

(18) is prepared from {2-[(7-Hydroxy-benzofuran-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (15) in an analogous manner to that described for the preparation of (5) example 1, step 4.

Step 2: 7-(3-Dimethylamino-propoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (17)

(17) is prepared from (2-{[7-(3-Dimethylamino-propoxy)-benzofuran-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (18) in an analogous

manner to that described for the preparation of (1) example 1, step 5; exact MW [M+H] calc'd: 354.18; MW found [M+H]: 354.2.

Example 7

7-(2-Diisopropylamino-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (19)

Step 1: (2-{[7-(2-Diisopropylamino-ethoxy)-benzofuran-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (20)

(20) is prepared from {2-[(7-Hydroxy-benzofuran-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (15) in an analogous manner to that described for the preparation of (5) example 1, step 4.

Step 2: : 7-(2-Diisopropylamino-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (19)

(19) is prepared from (2-{[7-(2-Diisopropylamino-ethoxy)-benzofuran-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (20) in an analogous manner to that described for the preparation of (1) example 1, step 5; exact MW [M+H] calc'd: 396.23; MW found [M+H]: 396.2.

Example 8

7-(2-Piperidin-1-yl-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (21)

Step 1: (2-{[7-(2-Piperidin-1-yl-ethoxy)-benzofuran-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (22)

(22) is prepared from {2-[(7-Hydroxy-benzofuran-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (15) in an analogous manner to that described for the preparation of (5) example 1, step 4.

Step 2: : 7-(2-Piperidin-1-yl-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (21)

(21) is prepared from (2-{[7-(2-Piperidin-1-yl-ethoxy)-benzofuran-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (22) in an analogous manner to that described for the preparation of (1) example 1, step 5; white solid; exact MW [M+H] calc'd: 380.20; MW found [M+H]: 380.2.

Example 9

7-(2-Pyrrolidin-1-yl-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (23)

Step 1: (2-{[7-(2-Pyrrolidin-1-yl-ethoxy)-benzofuran-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (24)

(24) is prepared from {2-[(7-Hydroxy-benzofuran-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (15) in an analogous manner to that described for the preparation of (5) example 1, step 4.

Step 2: 7-(2-Pyrrolidin-1-yl-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (23)

(23) is prepared from (2-{[7-(2-Pyrrolidin-1-yl-ethoxy)-benzofuran-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (24) in an analogous manner to that described for the preparation of (1) example 1, step 5; yellow solid; exact MW [M+H] calc'd: 366.18; MW found [M+H]: 366.2.

Example 10

7-(2-Morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (25)

Step 1: (2-{[7-(2-Morpholin-4-yl-ethoxy)-benzofuran-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (26)

(26) is prepared from {2-[(7-Hydroxy-benzofuran-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (15) in an analogous manner to that described for the preparation of (5) example 1, step 4.

Step 2: 7-(2-Morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (25)

(25) is prepared from [2-({5-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-benzo[b]thiophene-2-carbonyl}-amino)-phenyl]-carbamic acid tert-butyl ester (26) in an analogous manner to that described for the preparation of (1) example 1, step 5; yellow solid; exact MW [M+H] calc'd: 382.18; MW found [M+H]: 382.0.

Example 11

5-[2-(2-Methoxy-ethoxy)-ethoxy]-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (27)

Step 1: [2-({5-[2-(2-Methoxy-ethoxy)-ethoxy]-benzo[b]thiophene-2-carbonyl}-amino)-phenyl]-carbamic acid tert-butyl ester (28)

To a solution of 77mg (0.20mmol) {2-[(5-Hydroxy-benzo[*b*]thiophene-2-carbonyl)-amino]-phenyl}-carbamic acid *tert*-butyl ester (4) in 3ml acetonitrile was added 200 mg potassium carbonate and 0.3ml 1-bromo-2-(2-methoxyethoxy)-ethane. The reaction mixture was heated at 100°C for 90min and poured into brine. The aqueous phase was extracted with ethyl acetate and the organic phase was dried over sodium sulfate, the solvent was evaporated and the residue subjected to silica gel chromatography (petrolether/ethyl acetate 2:1 and then 1:1). The product (28) (80mg, 0.164mmol) was obtained as a colorless oil.

Step 2: 5-[2-(2-Methoxy-ethoxy)-ethoxy]-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (27)

A solution of 80mg (0.164mmol) of [2-({5-[2-(2-Methoxy-ethoxy)-ethoxy]-benzo[b]thiophene-2-carbonyl}-amino)-phenyl]-carbamic acid tert-butyl ester (28) in 1.0ml trifluoroacetic acid was stirred for 45min at room temperature and then added to an aqueous solution of sodium bicarbonate. After extraction with ethyl acetate and removal of the solvent the residue was recrystallized from ethyl acetate/ heptane to yield 40mg (0.103mmol) of the desired product (27) as white crystals, mp.167-168°C.

Example 12

5-(2-Methoxy-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (29)

Step 1: (2-{[5-(2-Methoxy-ethoxy)-benzo[b]thiophene-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (30)

(30) is prepared from {2-[(5-Hydroxy-benzo[*b*]thiophene-2-carbonyl)-amino]-phenyl}-carbamic acid *tert*-butyl ester (4) in an analogous manner to that described for the preparation of (28) example 11, step 1.

Step 2: 5-(2-Methoxy-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (29)

(29) is prepared from (2-{[5-(2-Methoxy-ethoxy)-benzo[b]thiophene-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (30) in an analogous manner to that described for the preparation of (27) example 11, step 2; yellow solid, mp. 162-165°C.

Example 13

7-[2-(2-Methoxy-ethoxy)-ethoxy]-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (31)

Step 1: [2-({7-[2-(2-Methoxy-ethoxy)-ethoxy]-benzofuran-2-carbonyl}-amino)-phenyl]-carbamic acid tert-butyl ester (32)

(32) is prepared from {2-[(7-Hydroxy-benzofuran-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (15) in an analogous manner to that described for the preparation of (28) example 11, step 1.

Step 2: 7-(2-Methoxy-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (29)

(31) is prepared from [2-({7-[2-(2-Methoxy-ethoxy)-ethoxy]-benzofuran-2-carbonyl}-amino)-phenyl]-carbamic acid tert-butyl ester (32) in an analogous manner to that described for the preparation of (27) example 11, step 2; exact MW [M+H] calc'd: 371.16; MW found [M+H]: 371.2.

Example 14

7-(2-Methoxy-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (33)

Step 1: (2-{[7-(2-Methoxy-ethoxy)-benzofuran-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (34)

(34) is prepared from {2-[(7-Hydroxy-benzofuran-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (15) in an analogous manner to that described for the preparation of (28) example 11, step 1.

Step 2: 7-(2-Methoxy-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (33)

(33) is prepared from (2-{[7-(2-Methoxy-ethoxy)-benzofuran-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (34) in an analogous manner to that described for the preparation of (27) example 11, step 2; exact MW [M+H] calc'd: 327.13; MW found [M+H]: 327.0.

Example 15

5-(2-Methoxy-ethoxy)-1H-indole-2-carboxylic acid (2-amino-phenyl)-amide (35)

Step 1: {2-[(5-Allyloxy-1H-indole-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (36)

(36) is prepared from 5-Allyloxy-1H-indole-2-carboxylic acid (Moody, C.J., J. Chem. Soc. Perkin Trans. 1 (1984) 1333-1337; Julia, M., and Lallemand, J.-Y., Bull. Soc. Chim. Fr. (1973) 2046-2057) in an analogous manner to that described for the preparation of (3) example 1, step 2; mp. 171-172°C.

Step 2: {2-[(5-Hydroxy-1H-indole-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (37)

To a solution of 3370mg (8.27 mmol) {2-[(5-Allyloxy-1H-indole-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (36) in 100ml methanol was added 5ml water, 750mg Pd (10% on C) and 300mg p-toluenesulfonic acid. After heating at reflux for 6h the reaction mixture was added to a 1:1 mixture of brine and

saturated $NaHCO_3$ solution. The aqueous phase was extracted twice with ethyl acetate and the combined organic phases were washed with brine, dried over Na_2SO_4 and filtrated over celite. The solvent was removed and the residue was subjected to silica gel chromatography (petrolether/ethyl acetate 2:1). {2-[(5-Hydroxy-1H-indole-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (37) was recrystallized from diethyl ether/petrol ether to yield 1265mg (3.44mmol) crystalls, mp. 197°C (decomposition).

Step 3: (2-{[5-(2-Methoxy-ethoxy)-1H-indole-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (38)

(38) is prepared {2-[(5-Hydroxy-1H-indole-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (37) in an analogous manner to that described for the preparation of (28), example 11, step 1.

Step 4: 5-(2-Methoxy-ethoxy)-1H-indole-2-carboxylic acid (2-amino-phenyl)-amide (35)

(35) is prepared: (2-{[5-(2-Methoxy-ethoxy)-1H-indole-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (38) in an analogous manner to that described for the preparation of (27) example 11, step 2; exact MW [M+H] calc'd: 326.15; MW found [M+H]: 326.3.

Example 16

5-(2-Hydroxy-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (39)

Step 1: [2-({5-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-benzo[b]thiophene-2-carbonyl}-amino)-phenyl]-carbamic acid tert-butyl ester (40)

To a solution of 96mg (0.25mmol) {2-[(5-Hydroxy-benzo[b]thiophene-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (4) in 5ml acetonitrile was added 120 mg potassium carbonate and 0.3ml (2-bromoethoxy)-tert-butyldimethylsilane. The reaction mixture was heated at reflux for 90min and at 85°C for 2h and poured into 5% aqueous citric acid. The aqueous phase was extracted with ethyl acetate and the organic phase was dried over sodium sulfate, the solvent was evaporated and the residue subjected to silica gel chromatography

(petrolether/ethylacetate 4:1 and then 9:1). [2-({5-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-benzo[b]thiophene-2-carbonyl}-amino)-phenyl]-carbamic acid tert-butyl ester (40) (63mg, 0.116mmol) was obtained as a colorless solid.

Step 2: 5-(2-Hydroxy-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (39)

To a solution of 55mg (0.100mmol) [2-({5-[2-(tert-butyl-dimethyl-silanyloxy)-ethoxy]-benzo[b]thiophene-2-carbonyl}-amino)-phenyl]-carbamic acid tert-butyl ester (40) in 5ml tetrahydrofurane was added 38mg (0.120mmol) tetra-n-butylammonium fluoride. The reaction mixture was stirred at room temperature for 1h and poured into brine. The aqueous phase was extracted with ethyl acetate and the combined organic phases were washed brine and dried over sodium sulfate. The solvent was evaporated and the residue of (2-{[5-(2-Hydroxy-ethoxy)-benzo[b]thiophene-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester was dissolved in 1.0ml trifluoroacetic acid. The reaction mixture was stirred for 45min at room temperature and then added to an aqueous solution of sodium bicarbonate. After extraction with ethyl acetate and removal of the solvent the residue was recrystallized from ethyl acetate/ diethyl ether to yield 17mg (0.052mmol) of 5-(2-Hydroxy-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (39) as a white solid, mp. 215-216°C.

Example 17

7-(2-Hydroxy-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (41)

Step 1: [2-({7-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-benzofuran-2-carbonyl}-amino)-phenyl]-carbamic acid tert-butyl ester (42)

(42) is prepared from {2-[(7-Hydroxy-benzofuran-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (15) in an analogous manner to that described for the preparation of (40) example 16, step 1; exact MW [M+H] calc'd: 327.13; MW found [M+H]: 327.0.

Step 2: 7-(2-Hydroxy-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (41)

(41) is prepared from [2-({7-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-benzofuran-2-carbonyl}-amino)-phenyl]-carbamic acid tert-butyl ester (38) in an analogous manner to that described for the preparation of (39) example 16, step 2; mp. 182-183°C.

Example 18

5-(2-Hydroxy-ethoxy)-1H-indole-2-carboxylic acid (2-amino-phenyl)-amide (43)

Step 1: [2-({5-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-1H-indole-2-carbonyl}-amino)-phenyl]-carbamic acid tert-butyl ester (44)

(44) is prepared from {2-[(5-Hydroxy-1H-indole-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (37) in an analogous manner to that described for the preparation of (40) example 16, step 1.

Step 2: 5-(2-Hydroxy-ethoxy)-1H-indole-2-carboxylic acid (2-amino-phenyl)-amide (43)

(43) is prepared [2-({5-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-1H-indole-2-carbonyl}-amino)-phenyl]-carbamic acid tert-butyl ester (44) in an analogous manner to that described for the preparation of (39), example 16, step 2; mp. 222-223°C.

Example 19

[2-(2-Amino-phenylcarbamoyl)-benzo[b]thiophen-5-yloxy]-acetic acid (45)

Step 1: [2-(2-tert-Butoxycarbonylamino-phenylcarbamoyl)-benzo[b]thiophen-5-yloxy]-acetic acid tert-butyl ester (46)

To a solution of 96mg (0.25mmol) {2-[(5-Hydroxy-benzo[*b*]thiophene-2-carbonyl)-amino]-phenyl}-carbamic acid *tert*-butyl ester (4) in 3ml ethyl acetate was added 140 mg potassium carbonate and 60mg (0.40mmol) tert-butyl chloroacetate. The reaction mixture was heated at reflux for 16h and poured into a saturated aqueous solution of ammonium chloride. The aqueous phase was

extracted with ethyl acetate and the organic phase was dried over sodium sulfate, the solvent was evaporated and the residue subjected to silica gel chromatography (petrolether/ethyl acetate 4:1). The product fraction was recrystallized from heptane/diethylether to yield 57mg (0.114mmol) [2-(2-tert-Butoxycarbonylamino-phenylcarbamoyl)-benzo[b]thiophen-5-yloxy]-acetic acid tert-butyl ester (46), mp.166°C.

Step 2: [2-(2-Amino-phenylcarbamoyl)-benzo[b]thiophen-5-yloxy]-acetic acid (45)

A solution of 48mg (0.096mmol) [2-(2-tert-Butoxycarbonylamino-phenylcarbamoyl)-benzo[b]thiophen-5-yloxy]-acetic acid tert-butyl ester (46) in 1.0ml trifluoroacetic acid was stirred at room temperature for 2h. 1ml 1.7M aqueous NaOH was added dropwise and and the precipitated colourless crystals were filtered off and washed twice with water and four times with diethyl ether. 38mg (0.96mmol) [2-(2-Amino-phenylcarbamoyl)-benzo[b]thiophen-5-yloxy]-acetic acid (45), mp.250°C (decomposition).

Example 20

[2-(2-Amino-phenylcarbamoyl)-benzofuran-7-yloxy]-acetic acid (47)

Step 1: [2-(2-tert-Butoxycarbonylamino-phenylcarbamoyl)-benzofuran-7-yloxy]-acetic acid tert-butyl ester (48)

(48) is prepared from {2-[(7-Hydroxy-benzofuran-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (15) in an analogous manner to that described for the preparation of (46) example 19, step 1, mp. 144-145°C.

Step 2: [2-(2-Amino-phenylcarbamoyl)-benzofuran-7-yloxy]-acetic acid (47)

(47) is prepared from [2-(2-tert-Butoxycarbonylamino-phenylcarbamoyl)-benzofuran-7-yloxy]-acetic acid tert-butyl ester (48) in an analogous manner to that described for the preparation of (45) example 19, step 2; mp.: 208-210°C.

Example 21

[2-(2-Amino-phenylcarbamoyl)-1H-indol-5-yloxy]-acetic acid (49)

Step 1 [2-(2-tert-Butoxycarbonylamino-phenylcarbamoyl)-1H-indol-5-yloxy]-acetic acid tert-butyl ester (50)

(50) is prepared from {2-[(5-Hydroxy-1H-indole-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (37) in an analogous manner to that described for the preparation of (46) example 19, step 1, mp. 193°C (decomposition).

Step 2: [2-(2-Amino-phenylcarbamoyl)-1H-indol-5-yloxy]-acetic acid (49)

(49) is prepared from [2-(2-tert-Butoxycarbonylamino-phenylcarbamoyl)-1H-indol-5-yloxy]-acetic acid tert-butyl ester (50) in an analogous manner to that described for the preparation of (45) example 19, step 2; mp.: >250°C (decomposition).

Example 22

5-(Pyridin-2-ylmethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (51)

Step 1: (2-{[5-(Pyridin-2-ylmethoxy)-benzo[b]thiophene-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (52)

To a solution of 77mg (0.20mmol) {2-[(5-Hydroxy-benzo[*b*]thiophene-2-carbonyl)-amino]-phenyl}-carbamic acid *tert*-butyl ester (4) in 3ml ethyl acetate was added 200 mg potassium carbonate and 56mg (0.22mmol) 2-(bromomethyl)pyridine, hydrobromide. The reaction mixture was heated at reflux for 10h and poured into brine. The aqueous phase was extracted with ethyl acetate and the organic phase was dried over sodium sulfate, the solvent was evaporated and the residue subjected to silica gel chromatography (petrolether/ethyl acetate 3:2) to yield (2-{[5-(Pyridin-2-ylmethoxy)-benzo[b]thiophene-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (52) (80mg, 0.168mmol) as colourless crystals.

Step 2: 5-(Pyridin-2-ylmethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (51)

A solution of 72mg (0.151mmol) of (2-{[5-(Pyridin-2-ylmethoxy)-benzo[b]thiophene-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (52) in 1.0ml trifluoroacetic acid was stirred for 45min at room temperature and then added to an aqueous solution of sodium bicarbonate. After extraction with ethyl acetate and removal of the solvent the residue was recrystallized from ethyl acetate to yield 33mg (0.88mmol) 5-(Pyridin-2-ylmethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (51) as white solid, mp. 205-207°C.

Example 23

7-(Pyridin-2-ylmethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (53)

Step 1: (2-{[7-(Pyridin-2-ylmethoxy)-benzofuran-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (54)

(54) is prepared from {2-[(7-Hydroxy-benzofuran-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (15) in an analogous manner to that described for the preparation of (52) example 22, step 1, exact MW [M+H] calc'd: 460.19; MW found [M+H]: 460.0.

Step 2: 7-(Pyridin-2-ylmethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (53)

(53) is prepared from (2-{[7-(Pyridin-2-ylmethoxy)-benzofuran-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (54) in an analogous manner to that described for the preparation of (51) example 22, step 2; mp.: 105-135°C.

Example 24

5-(2-Hydroxy-ethyl)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (55)

Step 1: {2-[(5-Bromo-benzofuran-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (56)

A mixture of 5290mg (21.95mmol) 5-Bromo-benzofuran-2-carboxylic acid (Owen, C.P., et al., J. Pharm. Pharmacol. 51 (1999) 427-434) and 20ml thionyl chloride

was heated at reflux for 4h. The excess thionyl chloride was evaporated, 20ml toluene were added and evaporated again. The residue was dissolved in 50ml dichloromethane and 2.0ml pyridine and a solution of 4373mg (21.0mmol) mono-boc-orthophenylenediamine in 30ml dichloromethane were added at 0°C. After 12h the precipitate was filtered off and washed with diethyl ether to give a first crop of 6550mg (15.2mmol) {2-[(5-Bromo-benzofuran-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (56). The solvent of the mother liquid was removed and 250ml ethyl acetate were added to the residue. The organic phase was washed with 5% aqueous citric acid, saturated aqueous sodium bicarbonate solution and brine and dried over Na_2SO_4. 50ml heptane were added to the solution and the solvent was evaporated to give another 1000mg of (2.32mmol) of {2-[(5-Bromo-benzofuran-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (56).

Step 2: {2-[(5-Vinyl-benzofuran-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (57)

To a mixture of 2027mg (4.7mmol) {2-[(5-Bromo-benzofuran-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (56) and 289mg (0.25mmol) $Pd(Ph_3)_4$ in 40ml toluene were added 1.84ml of a 5.4M solution of sodium methoxide in methanol and 957mg (5.2mmol) vinylboronic acid dibutyl ester and the solution was heated at 90°C for 3h. The reaction mixture was poured on 5% aqueous citric acid. Extraction with ethyl acetate, washing of the organic phase with brine. The organic phase was dried over sodium sulfate, the solvent was evaporated and the residue subjected to silica gel chromatography (petrolether/ethylacetate 2:1) to give 1530mg (4.04mmol) {2-[(5-Vinyl-benzofuran-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (57).

Step 3: (2-{[5-(2-Hydroxy-ethyl)-benzofuran-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (58)

A solution of 114mg (o.30mmol) {2-[(5-Vinyl-benzofuran-2-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (57), 5ml THF and 1.4ml of a 0.5M solution of 9-BBN in THF was stirred at rt for 4h. A solution of 86mg NaOH in 0.6ml water was added and stirring was continued for further 2h. The reaction mixture was washed with brine and the organic phase dried over sodium sulfate, the solvent was evaporated and the residue subjected to silica gel chromatography (petrolether/ethylacetate 1:1) to give 54mg (0.136mmol) (2-{[5-(2-Hydroxy-ethyl)-benzofuran-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (58).

Step 4: 5-(2-Hydroxy-ethyl)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (55)

To a solution of 75mg (0.189mmol) (2-{[5-(2-Hydroxy-ethyl)-benzofuran-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester (58) in 3ml THF were added 1892µl of 4M solution of HCl in dioxane. The reaction was stirred at 55°C for 2h. The solvent was evaporated, ethylacetate was added and the organic phase was washed with saturated aqueous sodium bicarbonate solution and brine and dried over Na_2SO_4. The solvent was removed to give 45mg (0.152mmol) 5-(2-Hydroxy-ethyl)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (55); exact MW calc'd [M+H]: 297.12; MW found [M+H]: 297.1.

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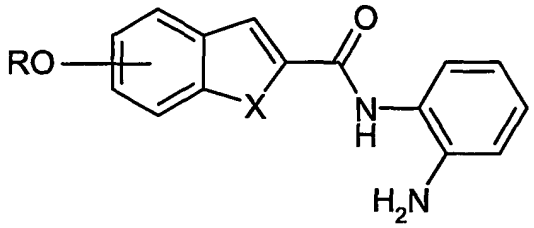
Patent Claims

1. A compound of formula I



formula I;

wherein

X represents N, S or O;

R represents CH_3-$(O\text{-}CH_2CH_2)_n$- or C_1-C_6-alkyl, which alkyl group is monosubstituted with
-CO_2H, -OH, R^1R^2N-, pyridin-2-yl, pyrrolidin-1-yl, piperidino or morpholino;
R^1, R^2 independently from each other denote C_1-C_6 alkyl;

n is 1, 2, 3 or 4;

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein

X represents N, S or O;

R represents R^1R^2N-C_1-C_6-alkyl and
R^1, R^2 are independently a C_1-C_6 alkyl group;

and pharmaceutically acceptable salts thereof.

3. A compound according to claim 2,

5-(2-Dimethylamino-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide,

5-(3-Dimethylamino-propoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide,
5-(3-Dimethylamino-propoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide
7-(2-Dimethylamino-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide, or
7-(2-Diisopropylamino-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide.

4. A compound according to claim 2,

7-(3-Dimethylamino-propoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide, or
5-(2-Diisopropylamino-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide.

5. A compound according to claim 1, wherein

X represents N, S or O;
R represents a group CH_3-(O-$CH_2CH_2)_n$-;
n is 1, 2, 3 or 4;

and pharmaceutically acceptable salts thereof.

6. A compound according to claim 5,

5-(2-Methoxy-ethoxy)-1H-indole-2-carboxylic acid (2-amino-phenyl)-amide,
5-(2-Methoxy-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
7-(2-Methoxy-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide,
7-[2-(2-Methoxy-ethoxy)-ethoxy]-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide or
5-[2-(2-Methoxy-ethoxy)-ethoxy]-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide.

7. A compound according to claim 1, wherein

X represents N, S or O;
R represents C_1-C_6-alkyl, monosubstituted with pyridin-2-yl, pyrrolidin-1-yl, piperidino or morpholino;

and pharmaceuically acceptable salts thereof.

8. A compound according to claim 7,

7-(Pyridin-2-ylmethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide,
5-(Pyridin-2-ylmethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
7-(2-Pyrrolidin-1-yl-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide,
7-(2-Piperidin-1-yl-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide or
5-(2-Morpholin-4-yl-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide.

9. A compound according to claim 1, wherein

X represents N, S or O;
R represents C_1-C_6-alkyl, monosubstituted with -CO_2H;

and pharmaceuically acceptable salts thereof.

10. A compound according to claim 9,

2-(2-Amino-phenylcarbamoyl)-benzofuran-7-yloxy]-acetic acid,
2-(2-Amino-phenylcarbamoyl)-benzo[b]thiophene-5-yloxy]-acetic acid or
2-(2-Amino-phenylcarbamoyl)-1H-indole-5-yloxy]-acetic acid.

11. A compound according to claim 1, wherein

X represents N, S or O;

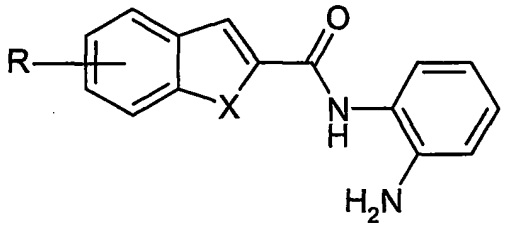
R represents C_1-C_6-alkyl, monosubstituted with OH;

and pharmaceuically acceptable salts thereof.

12. A compound according to claim 11,

5-(2-Hydroxy-ethoxy)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-(2-Hydroxy-ethoxy)-1H-indole-2-carboxylic acid (2-amino-phenyl)-amide
or
7-(2-Hydroxy-ethoxy)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide.

13. A compound of the formula I-A



(formula I-A),

wherein

X and R have the significance given in claim 1;

and pharmaceutically acceptable salts thereof.

14. Compounds of formula I-A, wherein

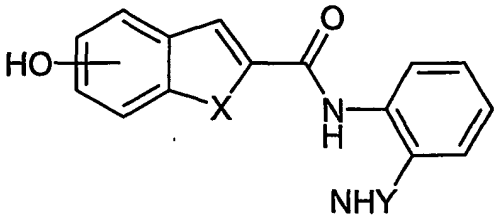
X represents O;
R is C_1-C_6-alkyl, which alkyl group is monosubstituted with -OH.

15. The compound according to claim 14,

5-(2-Hydroxy-ethyl)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide.

16. The process for the manufacture of a compound of formula I according to claim 1, comprising

a) reacting a compound of formula II



(formula II),

in which

X is as defined in claim 1; and
Y represents hydrogen or a suitable amino protecting group

with a compound of formula III

R-LG

(formula III),

in which

R has the meaning defined in claim 1; and
and reactive substituents, if present in R, are suitably protected;
LG is a suitable leaving group; and

b) subsequently if Y respesents a protected amino group, deprotection of this group as well as cleavage of protecting groups, if present, in R to give a compound of formula I; and

c) conversion, if desired, into its pharmaceutically acceptable salt.

17. A medicament containing one or more compounds as claimed in any one of claims 1 to 15 and pharmaceutically acceptable excipients.

18. A medicament according to claim 17 for the inhibition of tumor growth.

19. The use of a compound in any one of claims 1 to 15 for the treatment of cancer.

20. The use of a compound in any one of claims 1 to 15 for the manufacture of corresponding medicaments for the inhibition of tumor growth.

21. A compound according to any one of claims 1 to 15, whenever prepared by a process as claimed in claim 16 or by an equivalent method.

22. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/001045

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D333/70 C07D307/85 C07D307/86 C07D209/42 A61K31/34
A61K31/38 A61K31/40 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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P,Y	WO 03/011851 A (F. HOFFMAN-LA ROCHE AG) 13 February 2003 (2003-02-13) claims 1-9	1-22
A	GB 2 165 537 A (JOHN WYETH & BROTHER LTD.) 16 April 1986 (1986-04-16) claims 1-22	1-22

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° *Special categories of cited documents :*

"A" document defining the general state of the art which is not considered to be of particular relevance
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 September 2004	06/10/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax (+31–70) 340–3016	Herz, C

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/001045

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Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	US 5 395 849 A (M. D. WITTMAN ET AL.) 7 March 1995 (1995-03-07) claims 1-13	1-22
A	DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002297054 Database accession no. 4529791 abstract	1-22

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/001045

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

International Application No
PCT/EP2004/001045

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0847992 A	17-06-1998	DE 69729626 D1	29-07-2004
		EP 1437346 A1	14-07-2004
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